GLP-1: A Mediator of the Beneficial Metabolic Effects of Bariatric Surgery?

There has been increasing interest in the role that gut hormones may play in contributing to the physiological changes produced by certain bariatric procedures, such as Roux-en-Y gastric bypass and sleeve gastrectomy. Here, we review the evidence implicating one such gut hormone, glucagon-like peptide-1, as a mediator of the metabolic benefits of these two procedures.

Bariatric surgery is the most effective treatment for patients with severe obesity (body mass index of \( \geq 35.0 \) kg/m\(^2\)), both in terms of weight loss and improvements in obesity-related diseases such as Type 2 diabetes (T2D) (44, 135). In keeping with these marked health benefits, the number of patients undergoing bariatric surgery has reached unprecedented levels, with over 340,000 bariatric procedures undertaken in 2011 (18). The mechanisms underlying the beneficial effects of bariatric surgery are now the focus of a burgeoning field of research, with the aim of developing new therapies for obesity and T2D (56, 122). In this regard, there has been an increasing interest in the role that gut hormones may play in mediating the physiological changes produced by certain bariatric procedures, such as Roux-en-Y gastric bypass (RYGBP) and sleeve gastrectomy (SG) (86, 132). In this review, we discuss how a specific gut hormone called glucagon-like peptide-1 (GLP-1) could play a role in contributing to some of the multisystem benefits of these two procedures (FIGURE 1). We focus on key clinical research studies that address the role of GLP-1 in mediating beneficial effects of RYGBP and SG on glucose homeostasis, pancreatic \( \beta \)-cell function, and bodyweight, and also explore insights from animal models. Emerging roles of the GLP-1 system in cardiovascular protection (145), neuroprotection (54), as well as suppression of non-alcoholic fatty liver disease (NAFLD) (129), psoriasis (19, 53), and adipose tissue inflammation (52, 78) evoke biologically plausible links with other benefits of bariatric surgery (FIGURE 1). However, the mechanistic basis for effects of bariatric surgery on the cardiovascular system (4, 11), cognitive function (9), NAFLD (117), psoriasis (123), and adipose tissue inflammation (11, 76) are less extensively studied to date and thus are not reviewed here.

Bariatric Procedures and Their Metabolic Benefits

RYGBP is considered the “gold standard” bariatric procedure, with robust long-term clinical outcomes (44, 130, 136, 137). Long thought to primarily be a hybrid restrictive-malabsorptive procedure, an accumulating body of evidence strongly suggests that non-mechanical mechanisms, such as altered gut hormone responses, gut microbiota, or gut-brain interactions underlie the beneficial effects of RYGBP (84, 140). In the last 5 years, there has been a notable shift in the types of bariatric procedures being performed (18). Purely restrictive procedures such as adjustable gastric band (AGB) and vertical-banded gastroplasty have been superseded by SG. This trend now places SG (5% in 2008 to 28% in 2011) as the second most common procedure performed globally after RYGBP (47% in 2011). In contrast to AGB, both RYGBP (FIGURE 2A) and SG (FIGURE 2B) alter the anatomy of the normal gastrointestinal (GI) tract. RYGBP comprises the formation of a small proximal gastric pouch to which a loop of mid-jejunum is connected, creating alimentary, bilio-pancreatic, and common limbs (FIGURE 2A). Thus ingested nutrients bypass the majority of the stomach and upper small bowel (all of duodenum and proximal jejunum) and directly enter the mid-jejunum. Consequently, nutrients, which pass through alimentary limb, do not mix with pancreatic enzymes or bile acids, which pass through the bilio-pancreatic limb, until the common channel. SG involves removal of the gastric fundus and body, whereas the rest of the GI tract is left intact, resulting in an unaltered route of nutrient passage through the GI tract (FIGURE 2B). Of note, both procedures result in accelerated emptying of the gastric remnant (32, 55). However, SG and RYGBP appear to have divergent effects on small intestinal motility (32, 142). The enterohepatic recirculation of bile acids is altered after both RYGBP (116) and SG (101). Although the extent to which bile acid dynamics differ between procedures is unknown, one can surmise that, given the markedly contrasting functional anatomy of SG and RYGBP (FIGURE 2), differential mechanisms therein are at play for each procedure.

Until the advent of SG, RYGBP had been unravelled in terms of risk-benefit profile (110). Accordingly, the effectiveness of SG compared with
RYGBP has come under increasing scrutiny. RYGBP and SG lead to comparable long-term weight loss (~20–30% of body weight) (20, 130), most of which occurs during the first postoperative year (24). There is, however, a wide variability in this weight loss response, and up to ~20% of patients may experience either inadequate initial weight loss or clinically important weight regain (24). Apart from a few notable exceptions (e.g., gastro-esophageal reflux), improvements in obesity-related comorbidities are also comparable between procedures (154). Perhaps the most striking effects of these procedures are the rapid beneficial changes in glucose homeostasis and insulin secretion, which occur within days of the operation before any significant weight change (70) and are persistent over at least 3 years (130). In addition, the presence of insulin resistance, known to vastly improve after bariatric surgery (11), is a key predictor of the beneficial impact of bariatric surgery on mortality, cardiovascular events, and incidence of T2D, independent of weight loss (135).

Although the mechanisms promoting the sustained weight loss and T2D amelioration, after RYGBP and SG, remain incompletely understood (84), gut hormones have been consistently proposed as key effectors of the physiological changes induced by these procedures (86, 104, 107, 132). In this regard, there is accumulating evidence that enhanced secretion of GLP-1 makes an important contribution to these beneficial effects.

**Physiological GLP-1 Secretion and Action**

GLP-1 is a gut hormone secreted in response to nutrient ingestion by specialized intestinal enteroendocrine cells called L-cells (46). Specifically, arrival of ingested sugars, lipids, and proteins at the apical surface of L-cells results in direct stimulation of GLP-1 release (46) (FIGURE 2C).

**FIGURE 1.** Schematic diagram illustrating the multisystem benefits of bariatric surgery

Schematic diagram illustrating the multisystem benefits of bariatric surgery (all boxes), including the benefits likely to be mediated by GLP-1 (red coded), those potentially mediated by GLP-1 (orange coded), and those unlikely to be mediated by GLP-1 (blue coded). CVD, cardiovascular diseases; OSA, obstructive sleep apnoea; GERD, gastroesophageal reflux disease; BIH, benign intracranial hypertension; PCOS, polycystic ovary syndrome.
Among these macronutrients, sugars and lipids are more potent stimulators of GLP-1 secretion than proteins (105). There are, however, multiple other direct stimuli, including chemical, neural, and hormonal factors, in addition to indirect stimuli such as changes in gut motility and gut microbiota (23). Notable hormonal stimuli of GLP-1 secretion include insulin and autocrine/paracrine effects of GLP-1 itself (69). Other sources of GLP-1 release include neurons (82) and pancreatic islet α-cells (111), although the extent to which these contribute to circulating GLP-1 is unknown. The historical view that GLP-1 is primarily a distal gut hormone (73) has been recently challenged, and it is now recognized that GLP-1 is expressed in a major lineage of mature enteroendocrine cells found throughout the GI tract (38, 97).

GLP-1 is produced from posttranslational processing of pre-proglucagon encoded by the proglucagon (GCG) gene (23). Proglucagon gene expression is primarily regulated by insulin receptor signaling and effectors of the Wnt signaling pathway, such as T-cell transcription factors (TCFs) and β-catenin, in a cell-type-specific manner (65). Furthermore, pre-proglucagon processing via proteolytic cleavage by prohormone convertases 1 and 2 also occurs in a tissue-specific manner. Thus glucagon is primarily expressed in pancreatic α-cells, and GLP-1 and oxyntomodulin in L-cells (23). Throughout the intestine, GLP-1 is stored in L-cell granules in its biologically active forms, GLP-1(7–36) and GLP-1(7–37) (23), and invariably co-secreted with another peptide called peptide YY (PYY) (49). Once secreted, active GLP-1 is almost immediately degraded at position 9 by dipeptidyl peptidase-4 (DPP-4) (93), which is expressed on endothelial cells of capillaries draining the intestinal mucosa and also in a soluble circulating form.

**FIGURE 2.** Schematic diagram illustrating the anatomy of RYGBP and SG, and the mechanisms leading to GLP-1 secretion

A: In RYGBP, nutrients rapidly pass through the small gastric pouch, by-passing the majority of the stomach and upper small bowel and directly entering the mid-jejunum. Nutrients meet pancreatic enzymes and bile acids at the common channel only. B: In SG, the removal of the gastric fundus and body results in an unaltered route of nutrient passage through the GI tract. Both procedures result in accelerated gastric emptying and a rapid entry of undigested food into the jejunum. Consequently, there is enhanced direct contact of nutrients with the apical surface of L-cells (purple), interspersed among intestinal epithelial cells, resulting in Ca\(^{2+}\)-dependent stimulation of GLP-1 secretion into intestinal small blood vessels (C).
The role of GLP-1 in energy (99) and especially glucose homeostasis (36) is well documented. Interestingly, there is an uncanny overlap between the benefits of bariatric surgery and the suggested actions of GLP-1 (FIGURE 1). Along with glucose-dependent insulinoctropic polypeptide (GIP), which is secreted by intestinal K-cells, GLP-1 is now recognized as one of two key gut hormones responsible for enhancing the insulin response to nutrient ingestion (36). This is a phenomenon known as the “incretin effect,” usually defined in relation to glucose challenge as a mechanism by which insulin secretion is enhanced in response to oral glucose compared with insulin secretion in response to intravenous glucose, achieving the same systemic glucose concentrations but relevant to lipid and protein also (6, 36). GLP-1 is therefore termed an “incretin” hormone. Of key relevance to bariatric surgery, the contribution of GLP-1 to the incretin effect increases exponentially with increasing rate of glucose delivery to the intestine, whereas GIP appears to contribute more at low glucose delivery rates (88). Intriguingly, there is a strong heritable component to the GLP-1 response to glucose challenge (90). In addition, GLP-1 exerts glucoregulatory actions by delaying gastric emptying (29) and by glucose-dependent inhibition of glucagon secretion. Establishing a physiological role of GLP-1 as a gut-derived satiety factor has been less clear-cut. Intravenous administration of active GLP-1 to humans, achieving levels ~40 pM above peak postprandial levels but markedly below those evident postprandially in individuals with accelerated gastric emptying, results in increased satiety and reductions in food intake (42). However, the accompanying inhibition of gastric emptying induced by GLP-1 (29) could at least partially explain the anorectic effect of GLP-1 (113). This is important in the context of the aforementioned effects of both RYGBP and SG on gastric emptying (32, 55). In this regard, individuals who have undergone vagotomy do not experience reductions in food intake in response to exogenous GLP-1 and also have accelerated gastric emptying despite exaggerated GLP-1 secretion (113). Thus local GLP-1 action on vagal nerve afferents in the GI tract or central action on vagal efferents could underlie the role of GLP-1 as a satiety factor. Importantly, obese individuals remain sensitive to the anorectic effects of physiological levels of GLP-1 (43). The phenomenon of rapid GLP-1 inactivation by DPP-4 (93) points toward a greater relative importance of local rather than systemic actions in GLP-1 biology. Notably, pharmacological DPP-4 inhibition has no effect on GLP-1-induced gastric emptying (112), suggesting that local action immediately after secretion and before degradation by DPP-4 may be relatively more important for the physiological role of GLP-1 in control of energy balance in humans. Furthermore, GLP-1 is a candidate mediator of the “ileal brake” (131), a phenomenon whereby the presence of nutrients in the distal gut results in a reduction in GI motility, which in turn could also contribute to satiety indirectly (85). Nevertheless, there is strong evidence that circulating GLP-1 has appetite-suppressing effects through direct activation of energy homeostatic centers in the brain (27, 143).

T2D, Obesity, and GLP-1

Until relatively recently, the main clinical application for the GLP-1 system has related to its role in the pathophysiology and treatment of T2D. An impaired incretin effect is an early feature of T2D pathophysiology (6). However, in patients with T2D, this is now thought to be a secondary phenomenon characterized by defective insulotropism due to β-cell dysfunction rather than impaired GLP-1 secretion (6). Nevertheless, obesity is associated with a blunted GLP-1 response (99a), particularly evident with increasing BMI (141) and insulin resistance (41, 90). Insulin resistance in association with liver fat accumulation is closely related to impaired GLP-1 response, elegantly demonstrated in a study of young adult twins discordant and concordant for obesity (90). GLP-1-based pharmacotherapies are already a mainstay of treatment for T2D (83) and are often employed in a personalized approach to management for obese patients with T2D (58). Furthermore, the GLP-1 receptor (GLP-1R) agonist liraglutide (Victoza, Novo Nordisk, Bagsvaerd, Denmark) is an effective anti-obesity agent, and the license may soon be extended to include this indication also (87). Thus several characteristics, including nutrient-stimulated secretion from the intestine, physiological roles in pertinent metabolic responses, such as incretin and potentially satiety responses, and the success of GLP-1-based pharmacotherapies make GLP-1 biology a highly attractive target in the quest to unravel the mechanisms of bariatric surgery.

GLP-1 Responses After Bariatric Surgery

The first observations that circulating levels of gut proglucagon gene products increase after bariatric
surgery were made over 30 years ago. Fasting and postprandial proglucagon products levels were found to be elevated after jejunoileal bypass (JIB) (138), an intestinal rerouting procedure involving anastomosis of the proximal jejunum to distal ileum but now defunct. These increases in circulating proglucagon products were sustained for >20 years postoperatively (103). Although other products of the proglucagon gene have been less well studied in the context of bariatric surgery-induced changes (40, 74), interest in GLP-1 has progressively increased.

In the last 5 years, multiple prospective studies, randomized or case control in design, have described the characteristic GLP-1 response, which follows both RYGBP and SG:

1) Fasting GLP-1 levels after these procedures are not altered (109, 153), including compared with obese patients who experienced similar weight loss achieved by a low-calorie diet (1,300–1,800 kcal/day) (146) or by AGB (15).

2) Enhanced postprandial GLP-1 responses are observed even at 1–3 days postoperatively (40, 77).

3) Both total (40, 118, 121, 146) and active (109, 153) GLP-1 levels are enhanced.

4) The GLP-1 response is greater after RYGBP than after SG (approximately fivefold and threefold enhancement of preoperative response, respectively), as borne out by the vast majority of studies comparing these two procedures (109, 121, 152, 153).

5) The enhanced GLP-1 response was not observed in obese patients who were calorically restricted to mimic the postsurgery diet (39) or in obese patients who experienced similar weight loss achieved by a low-calorie diet (1,300–1,800 kcal/day) (146) or by AGB (15) in matched comparisons with patients who underwent RYGBP or SG.

6) There is a progressive increase in GLP-1 response during the first postoperative year (14, 40, 72); however, this is not a universal finding (109).

7) The enhanced GLP-1 responses persist in the long term (26).

8) Changes in GLP-1 secretion are in stark contrast to the relatively unaltered secretion of its incretin counterpart GIP (40, 50, 62).

9) The above findings (1–8) are also generalizable to patients with T2D (26, 63, 68, 70, 75, 96, 121, 152).

Mechanisms Underlying Enhanced GLP-1 Response

A number of methodological approaches have begun to elucidate the mechanisms for enhanced GLP-1 secretion after bariatric surgery. Bypass of a proximal gut (“foregut”) factor or increased distal gut (“hindgut”) L-cell nutrient exposure are two potential explanations for the altered gut hormone profile observed after RYGBP (132). However, the burden of evidence is in favor of the latter. First, enhanced GLP-1 responses are also observed after SG, despite the absence of alteration in the route of nutrient delivery (FIGURE 2B). Second, studies in patients who underwent JIB (see above) showed evidence of enteroendocrine cell hyperplasia within the bypass loop, including a significant increase in the number of enteroglucagon-containing cells (17). Although this has not been studied in patients who underwent RYGBP, a study in rats subjected to RYGBP (98) showed an increase in the number of L-cells in the Roux and common limbs but not in the bypassed biliopancreatic limb (FIGURE 2), invoking a direct link between nutrient stimulation and hindgut L-cell adaptation. The progressive increase in GLP-1 responses with time postoperatively could represent further evidence of this enteroendocrine cell-adaptive response (14); however, this cannot explain the acute changes in GLP-1 response postsurgery.

Either reduced proximal gut nutrient absorption or expedited nutrient delivery or both could theoretically underlie this enhanced hindgut L-cell exposure leading to enhanced GLP-1 responses. In support of this hindgut hypothesis, imaging studies using scintigraphic or cine magnetic resonance imaging techniques have demonstrated associations of exaggerated GLP-1 responses with faster gastric pouch emptying in the case of RYGBP (32) and enhanced intestinal motility following SG (142). Studies in RYGBP patients employing insertion of a gastrostomy tube in the remnant stomach, enabling the nutrient administration to the bypassed segments of the GI tract, further support the hindgut-driven enhancement of GLP-1 responses. Prospective crossover studies report a significantly greater effect of oral (jejunal, i.e., distal) delivery than gastrostomy tube (gastric, i.e., proximal) delivery on postprandial total (115) or active (79) GLP-1 levels in patients who underwent RYGBP, although this was not a universal finding (50). Furthermore, the exaggerated GLP-1 response and accompanying insulin hypersecretion, as seen in patients with hyperinsulinemic hypoglycemia after RYGBP (25, 124), can be reversed by reverting nutrient delivery from the distal gut back to the proximal gut via gastrostomy tube insertion (33, 91). Studies in animal models using a procedure called ileal transposition, in which the total length of the gut remained unaltered but a defined ileal segment is transposed with the proximal jejunum, provide a further layer of evidence that early exposure of distal intestinal epithelium to nutrients as seen in RYGBP and SG is sufficient to explain the enhanced GLP-1 responses (66, 106, 119).
There are a number of other mechanisms that could underlie the enhanced GLP-1 response. For example, reduced fasting DPP-4 activity has been observed after RYGBP but not with a calorically restricted control group (7). In this study, the change in DPP-4 activity did not correlate with nutrient-stimulated circulating GLP-1 levels, suggesting that a DPP-4-related mechanism for enhancing GLP-1 responses makes only a minor contribution if any to the effects of bariatric surgery on GLP-1 dynamics. Unfortunately, in this regard, there is a lack of studies measuring both total and active GLP-1. Interestingly, both vagotomy (113), known to be a variable feature of the RYGBP procedure (108), and duodenal removal (100) (as part of pylorus-preserving pancreatoduodenectomy) result in increased postprandial GLP-1 secretion. Alterations in bile acid flow or in gut microbiota could also contribute to changes in GLP-1 after surgery (84). Although circulating bile acid levels increase following RYGBP and SG, the time course of these changes is unclear. There are reports of delayed (1 yr postsurgery) rather than early onset (3 mo postsurgery) for the postoperative changes in circulating bile acids (5, 139). This brings into question the role of bile acids in mediating the postsurgery changes in GLP-1, which, as discussed above, occur early postsurgery. Limited data show that RYGBP and SG are associated with modification in microbiota with a shift to a “lean” microbiota phenotype (3, 12). However, it is unclear whether these changes contribute to the beneficial effects of these procedures or are a consequence of the marked changes that occur postsurgery. Thus the relationship of altered gut microbiota with GLP-1 responses postsurgery remains elusive.

Interestingly, the aforementioned non-bariatric manipulations, including jejunostomy (50), vagotomy (113), and duodenectomy (100), lead to a more rapid appearance of glucose in the circulation, which could potentially affect GLP-1 secretion (88) and thus confound the interpretation of the results of these studies. An alteration in glucose kinetics is also a well documented phenomenon in patients who have had RYGBP (61, 120) or SG (146), but not AGB (120). This altered plasma glucose profile is characterized by an earlier higher postprandial peak followed by a sustained reduction, with overall area under the curve (AUC) unchanged (61, 120, 146), and is also evident in patients with T2D (70). The potential importance of altered glucose kinetics to GLP-1 responses was highlighted in a study by Breitman et al. (16), which compared nutrient delivery by either nongastric (NG) or nasojunal (NJ) tubes in nonsurgical glucose-tolerant obese subjects. In this crossover study, glucose excursions obtained with NG and NJ delivery were replicated using isoglycemic glucose infusions. This enabled calculation of the relative contribution of the GI tract to postprandial glucose disposal by comparing the amount of glucose required to match plasma glucose curves obtained following NG and NJ delivery. Compared with NG delivery, there was a more rapid glucose appearance in plasma (by ~20 min), a sixfold greater GLP-1 response, and a twofold increase in the contribution of the GI tract to glucose disposal with the NJ route. This study elegantly portrays the complex relationship between altered glucose kinetics and GLP-1 response following enhanced hindgut delivery of glucose.

Although the precise mechanisms underlying the enhanced GLP-1 response after bariatric surgery remain to be fully elucidated, the link between enhanced hindgut nutrient delivery and GLP-1 secretion is clear. However, perhaps a more important question is whether this enhanced GLP-1 response can account for clinically important metabolic changes, such as improvements in glucose homeostasis and sustained weight loss.

Role of GLP-1 in Glucose Homeostasis and Islet Cell Function After Bariatric Surgery

The revelation that there could be a surgical cure for T2D (114) triggered the development of a novel field of metabolic research, which is still thriving two decades later. The benefits of bariatric surgery over standard medical care for obese patients with T2D have since become apparent in an expanding number of randomized trials (57, 94, 130). Restoration of β-cell function following nutrient challenge is the critical mechanism underlying the long-term benefits after RYGBP (37, 70, 127). Taken together with both the success of GLP-1-based therapy in the treatment of T2D and known enhancement of GLP-1 response following RYGBP and SG, there has been increasing interest in the role of GLP-1 in mediating these remarkable effects.

There are, however, several challenges in dissecting out the contribution of GLP-1 to glucose homeostasis and β-cell function after RYGBP and SG. First, bariatric surgery is often preceded by a period of caloric restriction to reduce liver size before the operation, and postoperatively patients invariably resume a low-calorie diet due to a combination of preoperative counseling, effects of wound healing, and the appetite-suppressing effects of these procedures (92). Indeed, multiple studies (15, 59, 60, 80, 81, 152) have demonstrated that the early postoperative changes in glucose homeostasis and/or insulin sensitivity could be explained by postoperative caloric restriction alone...
However, it is clear that caloric restriction cannot account for alterations in insulin secretion observed after RYGBP and SG (70, 75). Second, measurements of insulin sensitivity based on the oral glucose tolerance test are not validated in patients who have had bariatric surgery (34) and who therefore exhibit the attendant alterations in glucose kinetics as discussed above. Furthermore, there are rapid increments in insulin secretion during the first hour after nutrient challenge in subjects post-RYGBP or SG, with a subsequent gradual reduction in insulin and thus no overall change in AUC (34). Therefore, studies reporting changes in insulin sensitivity based only on the OGTT or studies with infrequent sampling during the first hour postmeal must be interpreted with caution. Third, assessment of β-cell reserve, for example by measuring fasting c-peptide, which is known to predict T2D remission after RYGBP (1), is seldom documented. This could be important in specific studies comparing GLP-1 responses in patients with varying degrees of glucose tolerance (96) or in diabetic patients with subsequent varying degrees of diabetes remission (51, 63). Fourth, the variance in GLP-1 response increases significantly with time after surgery (147), thus making it more difficult to adequately power long-term postoperative studies. Finally, the findings may not be generalizable to patients who have had SG (70), since most of the studies focus on RYGBP.

Nevertheless, there are several lines of evidence supporting a key role for GLP-1 in mediating the sustained improvements in glycemic control observed after RYGBP and SG. First, long-term restoration of β-cell function after RYGBP occurs only with oral glucose challenge and not with iso-glycemic intravenous challenge in patients with T2D (37). This highlights the importance of the incretin effect, and thus also GLP-1 as the predominant contributor to this phenomenon at high rates of nutrient delivery to the distal GI tract (88), in promoting β-cell function after RYGBP. Second, mechanistic studies in severely obese non-diabetic subjects help to shed light on the importance of GLP-1 in mediating an exaggerated effect on β-cell function by removing the confounding factor of hyperglycemia. For example, postprandial changes in circulating active GLP-1 levels were found to be tightly correlated with exaggerated positive changes in β-cell function in non-diabetic subjects who underwent RYGBP (10). Dirksen et al. (31) demonstrated, again in glucose-tolerant subjects, that insulin hypersecretion after RYGBP is dependent on oral nutrient delivery. Furthermore, using GLP-1 infusions to mimic the high circulating GLP-1 levels in the postprandial post-RYGBP state,
the investigators showed evidence of an enhanced and undimining insulinotropic effect of GLP-1, illustrating that pancreatic β-cells remain highly responsive to elevated GLP-1 levels post-RYGBP. Third, in patients with T2D, preoperative meal-mimic GLP-1 response is one of the strongest predictors of T2D remission at 1 year post-RYGBP or SG (102), and of long-term restoration of β-cell function post-RYGBP (37).

Finally, studies employing the GLP-1R antagonist exendin(9–39) provide the most robust evidence for a role of GLP-1 in mediating the changes in insulin secretion and thus contributing to improved glycemic control after RYGBP. Although these studies vary considerably in study population, study design, and dose of exendin(9–39) (Table 1), there are overriding messages conveyed in their results. First, the exaggerated postprandial GLP-1 response is confirmed as the central driver of hyperglycemia (125, 126), which is a well documented phenomenon known to develop in the long term after RYGBP (124). In this regard, exendin(9–39) could be employed as an effective therapy for patients who develop this complication of RYGBP. Finally, GLP-1 does not contribute to the suppression of endogenous glucose production or to glucose disposal after the documented rapid systemic glucose appearance (134) but retains inhibitory effects on glucagon secretion, albeit in the context of the paradoxical hyperglucagonemia observed post-RYGBP (67).

### Role of GLP-1 in Weight Loss After Bariatric Surgery

Although evidence from clinical research for a role of GLP-1 in improving glucose homeostasis and β-cell function abounds, there is a dearth of clinical studies investigating the potential for GLP-1 to mediate appetite changes and weight loss after bariatric surgery. Evidence for a link between GLP-1 response and weight loss is at best correlative, and a causal relationship has not yet been established. Given that both SG and RYGBP result in accelerated gastric emptying (32, 55) and that the role of GLP-1 in control of energy balance may involve its inhibitory effects on gastric emptying (113), the basis for a link between GLP-1 responses and weight loss after bariatric surgery is questionable. Nevertheless, in two observational studies that stratified RYGBP patients according to

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**Table 1. Summary of experimental studies employing Exendin(9–39) in RYGBP patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>Time post-RYGBP, yr</th>
<th>Ex-9 (Bolus + Infusion)</th>
<th>Experimental Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiménez et al., 2013 (64)</td>
<td>8 in T2D remission post-GBP</td>
<td>54 ± 8</td>
<td>31 ± 5</td>
<td>&gt;2</td>
<td>7,500 pmol/kg + 750 pmol · kg⁻¹ · min⁻¹ or saline</td>
<td>SLM test (398 kcal)</td>
</tr>
<tr>
<td>Jorgensen et al., 2013 (67)</td>
<td>9 with T2D pre- and post-GBP</td>
<td>47 ± 11</td>
<td>21 ± 1</td>
<td>Pre-op</td>
<td>43,000 pmol/kg + 900 pmol · kg⁻¹ · min⁻¹ or saline</td>
<td>SLM test (300 kcal) + gastric emptying</td>
</tr>
<tr>
<td>Shah et al., 2014 (134)</td>
<td>12 without T2D post-GBP</td>
<td>42 ± 2</td>
<td>33 ± 1</td>
<td>3 mo</td>
<td>1,700 pmol/kg + 300 pmol · kg⁻¹ · min⁻¹ or saline</td>
<td>SLM test (220 kcal) with dual tracing + infusion of labeled glucose</td>
</tr>
<tr>
<td>Saleh et al. 2014 (125)</td>
<td>7 non-hypo post-GBP</td>
<td>48 ± 3</td>
<td>34 ± 3</td>
<td>1 wk</td>
<td>7,500 pmol/kg + 750 pmol · kg⁻¹ · min⁻¹ or saline</td>
<td>SLM test (350 kcal) with dual glucose tracing</td>
</tr>
<tr>
<td>Saleh et al., 2011 (126)</td>
<td>9 hypo post-GBP</td>
<td>45 ± 5</td>
<td>31 ± 3</td>
<td>26 ± 1</td>
<td>3 mo</td>
<td>3.6 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>35 ± 3</td>
<td>33 ± 1</td>
<td>3.9 ± 0.5</td>
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<tr>
<td></td>
<td>47 ± 2</td>
<td>33 ± 1</td>
<td>3.3 ± 0.3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>39 ± 2</td>
<td>32 ± 2</td>
<td>3.7 ± 0.4</td>
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Age and body mass index (BMI) are expressed as means ± SE. Ex-9, exendin(9–39); GBP, gastric bypass; SLM, standard liquid meal; hypo, recurrent hypoglycemia.
weight-loss response, the mean GLP-1 response was ~50% higher in the “good responders” than in the “poor responders,” with proportionate relative reductions in appetite (35, 77). Interestingly, the differences between good and poor responders were more pronounced for GLP-1 than for PYY, a gut hormone thought to have a more predominant role in regulation of energy balance (86) in both of these studies. In contrast, GLP-1 responses do not appear to affect resting energy expenditure after RYGBP (35). Further research is required to investigate whether the mechanisms underlying changes in the thermic effect of food observed after RYGBP (149) could involve GLP-1. In a study of patients with T2D post-RYGBP, suppression of the orexigenic gut hormone ghrelin after a mixed meal was found to be highly correlated with peak postprandial GLP-1 and weight loss at 1 year postoperatively (128), suggesting that a gut hormone system effect is present after RYGBP and plays a role in mediating weight loss. Translational studies, using animal models, may perhaps offer a better opportunity to examine the weight loss effects of enhanced GLP-1 responses after bariatric surgery.

Insight From Animal Models

A number of interesting findings pertaining to the putative role of GLP-1 in mediating the beneficial effects of bariatric surgery have recently evolved through animal research. Although animal studies using models of bariatric surgery should be interpreted with caution due to differences in the rodent stomach and in rodent feeding (133) as well as the occurrence of model- and measure-dependent findings (89), this body of research has opened up avenues of investigation that cannot be readily reached through clinical research alone. Perhaps the exemplar of these translational studies, by Habegger et al. (48), demonstrated that response to a GLP-1R agonist (exendin-4), administered to rats before RYGBP, could predict failure to improve glucose tolerance but did not predict weight loss after RYGBP. This study paves the way for similar studies in humans, offering hope of a more personalized approach to patient counseling and potentially patient selection for bariatric surgery. Further studies employing the GLP-1R antagonist exendin(9–39) emphasize the important contribution that enhanced GLP-1 responses could make in regulating glucose homeostasis after RYGBP or SG (21, 71) and also confirm that GLP-1 has a more important role in influencing feeding behavior than energy expenditure after RYGBP (2). However, studies utilizing models of functional GLP-1R inactivation (95, 150, 151) are difficult to interpret due to the confounding effects of lower body weight in GLP-1R knockout mice and the central nervous system-specific role of GLP-1 (82).

Summary

Evidence from clinical research, using an array of innovative approaches, has provided a strong basis for GLP-1 as a key physiological mediator of the improvements in T2D after specific bariatric procedures. The role of enhanced GLP-1 responses in enhancing glucose homeostasis is somewhat clouded by effects of caloric restriction in the early postoperative setting and by the effects of weight loss in the late postoperative setting. Nevertheless, a dominant effect of exaggerated GLP-1 responses on β-cell function is evident at all stages postoperatively. The greater GLP-1 response observed after RYGBP compared with SG could underlie the apparent difference in T2D improvements between the two procedures (130). Therefore, understanding both the common and the distinct mechanisms governing responses to each of these procedures could yield valuable insights into novel pathways for treatment of obesity-related metabolic dysfunction. The goal of this field of research is to develop novel therapies that could mimic the gut hormone milieu induced by metabolic surgery. This is now a major avenue of drug development for treatment of T2D and obesity (56); for example, systemic administration of gut hormone combinations (122), such as a GLP-1/PYY and GLP-1/glucagon, are in early phases of development. However, postoperative hormonal changes within the hepatopancreatic system are likely to be of greater importance than alterations in systemic levels. A medical solution to reproducing the gut hormone response observed after bariatric surgery in the portal circulation, opposed to systemically, could be a more progressive approach. For example, orally administered G-protein-coupled bile acid receptor-1 agonists have recently been employed as L-cell activators (30). Understanding the complex interplay between GLP-1 and its counterpart PYY, as well as their hepatopancreatic dynamics, could also lead to more effective gut hormone-based therapies for T2D and obesity. Other important focus points for future research include whether the enhanced GLP-1 responses observed after these metabolic procedures could translate to enhanced β-cell mass (148). Although, in this regard, the long-term persistence of β-cell dysfunction in the setting of intravenous glucose challenge in patients
“cured” of T2D after bariatric surgery suggests that this GLP-1 effect is limited to enhancement of insulin secretion (37). Further mechanistic studies using specific GLP-1R antagonists or ideally specific antagonists of GLP-1 secretion coupled with functional GI- and neuro-imaging could add valuable insights into GLP-1 biology.

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References


38. Egerod KL, Engelstoft MS, Grunddal KV, Nørskov LS, Holst JJ, Worm D. Enteroincret peptide GLP-1 analogues promote early satiety and suppresses food intake by 10.220.33.3 on July 5, 2017 http://physiologyonline.physiology.org/ Downloaded from


